

PROCESS FOR PURIFICATION OF ZOLEDRONIC ACID

5

CROSS-REFERENCE TO RELATED APPLICATION

10 This application claims the benefit of the U.S. Provisional Application
Serial No. 60/449,837, filed February 27, 2003, the content of which is
incorporated herein.

FIELD OF THE INVENTION

15 The invention relates to processes for preparing and purifying zoledronic acid.

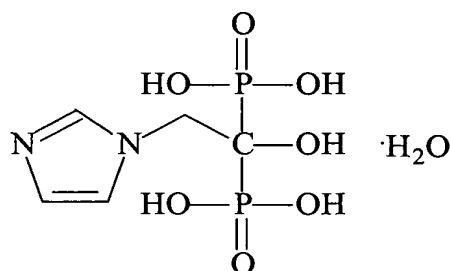
BACKGROUND OF THE INVENTION

20 Zoledronic acid is a third-generation bisphosphonate characterized by a side chain
that includes an imidazole ring. It inhibits osteoclast bone resorption and is used for the
treatment of tumor-induced hypercalcemia. Zometa® (Zoledronic acid for injection) is
indicated for the treatment of patients with multiple myeloma and patients with
documented bone metastases from prostate cancer, lung cancer, breast cancer and other
solid tumor types, in conjunction with standard antineoplastic therapy. Zometa® is
25 available in vials as a sterile powder for solution for intravenous infusion. One vial
contains 4mg of Zoledronic acid (anhydrous), corresponding to 4.264mg of Zoledronic
acid monohydrate.

Early studies, supported by Novartis (the manufacturer of both Pamidronate and
Zoledronic acid), have indicated that Zoledronic acid is more potent and probably more
30 effective than earlier drugs in this general class, including Etidronate, Alendronate and
Pamidronate. Furthermore, because of the lower dose required, it can be safely
administered over a much shorter period of time.

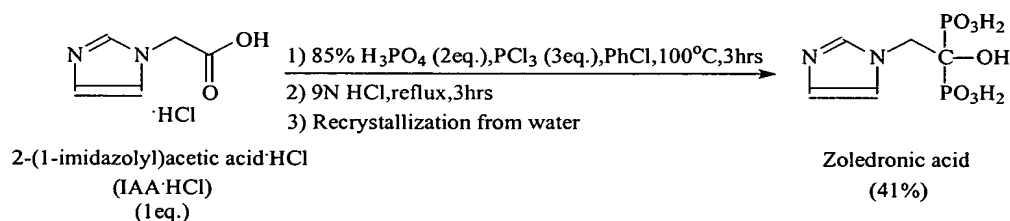
The empirical formula for Zoledronic acid monohydrate is: $C_5H_{10}N_2O_7P_2 \cdot H_2O$.

The chemical name of Zoledronic acid is 2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonic acid. The chemical structure of Zoledronic acid monohydrate is the following:



5 Zoledronic acid is a white crystalline powder. The melting point of Zoledronic acid is 239°C (dec.). It is highly soluble in 0.1N Sodium hydroxide solution, sparingly soluble in water and 0.1N Hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of Zoledronic acid in water is approximately 2.0.

10 US 4,939,130 discloses zoledronic acid and a process for making zoledronic acid, based on a per-se known method that was published by Kabachnick et. al. [Izv. Akad. Nauk. USSR, Ser. Khim., 2, 433-437, (1987)], (see example 10):



15 The final step of recrystallization from water (3) is the purification step that gives Zoledronic acid monohydrate.

SUMMARY OF THE INVENTION

20 The invention provides a process for the purification of crude Zoledronic acid by alkalization and re-acidification of an aqueous solution of Zoledronic acid.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "suspension" means undissolved particles in a liquid.

Crude Zoledronic acid may be purified and made in a process that includes alkalization and re-acidification of an aqueous solution of Zoledronic acid. In particular, the process entails mixing crude Zoledronic acid in water, preferably 10-26 volumes of water per grams of zoledronic acid, more preferably 10-15 volumes of water per grams of zoledronic acid. The mixing may be done at room temperature. The pH of the mixture is adjusted until a clear solution having an alkaline pH, preferably between 9-12, is obtained. The pH of the mixture may be adjusted by adding a base such as sodium hydroxide, potassium hydroxide, etc. The alkaline solution is acidified, preferably to a pH of less than 2, more preferably to PH between 1-1.5. The solution may be acidified by adding an acid, such as HCl, preferably 32% aqueous HCl. The acid causes zoledronic acid to precipitate and the precipitate is isolated.

The impurity profile of the purified Zoledronic acid vs. crude Zoledronic acid is as follows:

MS-425 (crude, no recrystallization) HPLC data (% on area)	LB-295 (cryst.) HPLC data (% on area)
RRT 0.84=0.57%	RRT 0.84=0.08%
RRT 1.00 (ZLD-Ac ¹)=97.20%	RRT 1.00 (ZLD-Ac)=99.60%
RRT 1.30=0.61%	RRT 1.30=ND ²
RRT 1.90 (IAA ³)=0.73%	RRT 1.90 (IAA)=ND
RRT 2.40 (Imidazole ⁴)=0.37%	RRT 2.40 (Imidazole)=ND

Notes:

³IAA is the starting material for the preparation of Zoledronic acid

⁴Imidazole is the starting material for the preparation of IAA

¹ZLD-Ac = Zoledronic acid

5 ²ND = not detected

HPLC method:

Column & Packing: Phenomenex, Luna 5 micron, Phenyl-Hexyl, 250*4.6

10 Eluent: 20% MeOH, 80% Buffer (990ml water, 10ml HClO₄ (~70%), 1ml H₃PO₄(~85%),
40 mmole/L 1-octanesulfonic acid sodium salt)

Flow: 0.8ml/min

15 Detection wave length: 220nm

Column Temperature: 30 degrees C

Diluent: 10% MeOH, 90% water

20

Sample concentration: 1mg/1ml diluent

Injection volume: 10 microlitter

25 The subject purification and the process for preparing zolendronic acid can also be
performed on an industrial scale.

30 The inventive process is advantageous compared to a simple recrystallization of
crude Zoledronic acid from water as the amount of water that is needed is significantly
smaller (while a recrystallization process from water is performed at reflux temperature in
order to achieve complete dissolution of the material in water). These two parameters
may be even more significant when an industrial production is concerned.

35 **EXAMPLES**

The present invention can be illustrated in one of its embodiments by the
following non-limiting examples.

Example 1

Crude Zoledronic acid (4g) was suspended in water (40ml) at room temperature. The pH of the suspension was adjusted to 9-10 by adding sodium hydroxide (pearls, 1.7g) to obtain a clear solution. Then the pH of the solution was adjusted to 1-1.5 to obtain a massive precipitation of Zoledronic acid. The obtained suspension was cooled to 5°C and was stirred at this temperature for an additional 2.5 hours. The product was then isolated by filtration, washed with water (1x10ml) and dried in a vacuum oven at 50°C for 22 hours to obtain 3.0g (75%) of recrystallized Zoledronic acid monohydrate.

Example 2

Zoledronic acid (200.0g) was suspended in water (2000ml) at room temperature. The pH of the suspension was adjusted to 14 by adding sodium hydroxide (pearls, 91.0g) to obtain a clear solution. Then the pH of the solution was adjusted to 1 by adding 32% HCl (300ml). The solution was cooled to 5°C and was stirred at this temperature for 2.5 hours. A massive precipitate of Zoledronic acid was observed at 20°C. The product was then isolated by filtration, washed with water (3x100ml) and dried in a vacuum oven at 50°C for 1.5 hour and then in a vented oven at 65°C for 24 hours to obtain 162.0g (81%) of recrystallized Zoledronic acid.

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications. All references mentioned herein are incorporated in their entirety.